Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Jeffrey E. Russel Examiner #: 62785 Date: 2-3-2005

Art Unit: 1654 Phone Number ~~3~~ 571-272-0969 Serial Number: 10/001,945

Mail Box and Bldg/Room Location: REN 3C18 (mailbox), 3D19 (office) Results Format Preferred (circle): PAPER (DISK) E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Modulation of Angiogenesis

Inventors (please provide full names): G. Olson, C. Self, L. Lee, C. Cook, J. Bicktoft, B. Morgan, C. Arico-Muendel

Earliest Priority Filing Date: 11-1-2001

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search SEQ ID NO:16 (PXAXXHA) in STN, in the U.S. patent application sequence database (pending, issued, & published), and in Geneseq/Swissprot/PIR. Please require ~~[redacted]~~ the sequence length to be 100 or fewer residues.

Thank you.

JER

Russel
10/001945

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=> d 13 que stat;fil hcaplus;s 13
L1              STR
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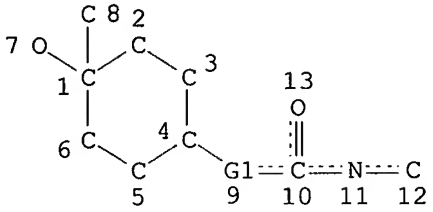


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  13

STEREO ATTRIBUTES: NONE
L3          127 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED   1834 ITERATIONS                    127 ANSWERS
SEARCH TIME: 00.00.01



COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
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FULL ESTIMATED COST                               162.19     162.40

FILE 'HCAPLUS' ENTERED AT 11:20:28 ON 04 FEB 2005
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 4 Feb 2005  VOL 142 ISS 6
FILE LAST UPDATED: 2 Feb 2005  (20050202/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L4          23 L3

=> e angiogensis/ct
E#   FREQUENCY    AT     TERM

Searched by: Mary Hale 571-272-2507 REM 1D86
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E2            0      2      ANGIOGENIN RECEPTORS/CT
E3            0        --> ANGIOGENSIS/CT
E4            0      2      ANGIOGRAPHY/CT
E5            0      2      ANGIOHEMOPHILIA/CT
E6            0      1      ANGIOIMMUNOBLASTIC/CT
E7            0      2      ANGIOIMMUNOBLASTIC LYMPHADENOPATHY/CT
E8            1      1      ANGIOKERATOMA/CT
E9            1      2      ANGIOKERATOMA CORPORIS DIFFUSUM/CT
E10           1             ANGIOMA/CT
E11           1             ANGIOMATOSIS/CT
E12           0      1      ANGIONEUROTIC/CT

=> s l4 and angiogens?
            48 ANGIOGENS?
L5           0 L4 AND ANGIOGENS?

=> d 1-23 cbib abs hitstr l4

L4   ANSWER 1 OF 23  HCAPLUS  COPYRIGHT 2005 ACS on STN
2004:98932   Document No. 140:271094  Stereocontrolled synthesis of
     8,11-dideoxytetrodotoxin, an unnatural analogue of puffer fish toxin.
     Nishikawa, Toshio; Urabe, Daisuke; Yoshida, Kazumasa; Iwabuchi, Tomoko;
     Asai, Masanori; Isobe, Minoru (Laboratory of Organic Chemistry, Graduate
     School of Bioagricultural Sciences, Nagoya University, Nagoya, 464-8601,
     Japan).  Chemistry--A European Journal, 10(2), 452-462 (English) 2004.
     CODEN: CEUJED.  ISSN: 0947-6539.  OTHER SOURCES: CASREACT 140:271094.
     Publisher: Wiley-VCH Verlag GmbH & Co. KGaA.
GI
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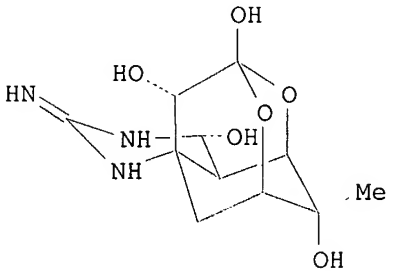

I

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AB   8,11-Dideoxytetrodotoxin (I), an unnatural tetrodotoxin analog, was
     synthesized in a highly stereoselective manner from a common intermediate
     from our synthetic studies on tetrodotoxin.  The key features in the
     synthesis were as follows: neighboring group participation of a
     trichloroacetamide to allow regioselective and stereoselective
     hydroxylation, protection of a δ-hydroxylactone as an ortho ester,
     and guanidine installation through the use of Boc-protected isothiourea.
     Global deprotection of the fully protected intermediate under acidic
     conditions gave 8,11-dideoxytetrodotoxin, which exhibited very weak biol.
     activities.
IT   674793-04-5P
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (stereocontrolled synthesis of 8,11-dideoxytetrodotoxin)
RN   674793-04-5  HCAPLUS
CN   Urea, N-[(1S,3S,3aR,4R,5R,6S,7aS)-5,6-bis(acetyloxy)hexahydro-3-methoxy-5-
     methyl-9-oxo-4,1-(epoxymethano)isobenzofuran-7a(1H)-yl]-N'-(phenylmethyl)-

Searched by: Mary Hale 571-272-2507 REM 1D86
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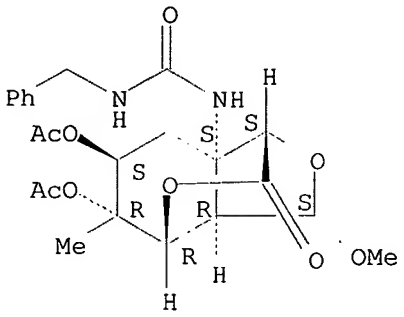
(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L4 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

2003:5795 Document No. 138:78455 Ointments containing polyalkylene glycol derivative-modified biologically active polypeptides. Yamasaki, Motoo; Suzawa, Toshiyuki; Murakami, Tatsuya; Sakurai, Noriko (Kyowa Hakko Kogyo Co., Ltd., Japan). PCT Int. Appl. WO 2003000278 A1 20030103, 165 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP6227 20020621. PRIORITY: JP 2001-190330 20010622.

AB Disclosed are ointments containing a chemical modified physiol. active polypeptide, wherein the chemical modified physiol. active polypeptide is exemplified by a physiol. active polypeptide chemical modified with at least one polyalkylene glycol, and the physiol. active polypeptide to be chemical modified is exemplified by superoxide dismutase, interferon-α, interferon-β, interferon-γ and granulocyte colony-stimulating factor. A polyethylene glycol cyclohexane derivative was prepared, and its N-hydroxysucinimide ester was reacted with recombinant human interferon-β. The modified interferon-β showed excellent antivirus activity in FL cells. Also, an ointment containing modified interferon-β showed improved storage stability as compared with unmodified interferon-β-containing ointment.

IT **445389-29-7P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

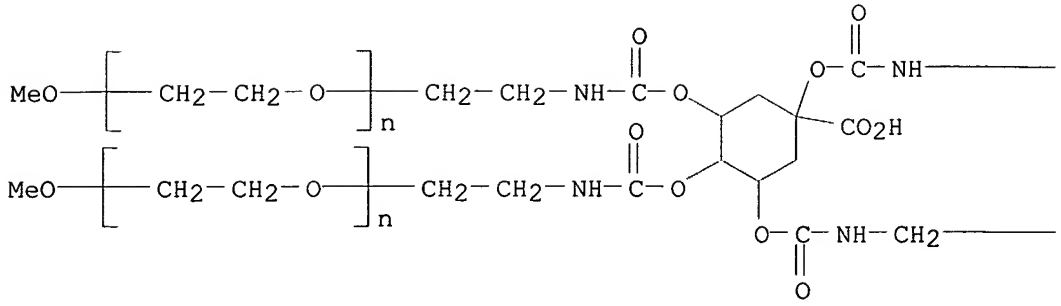
(preparation of polyalkylene glycol derivative-modified biol. active polypeptides for ointments)

RN 445389-29-7 HCAPLUS

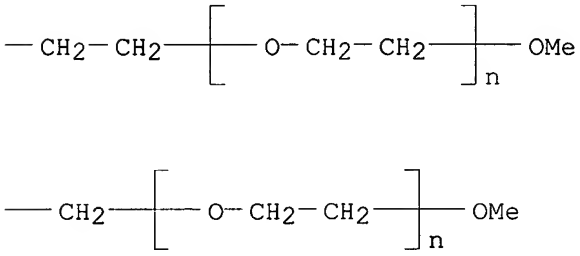
CN Poly(oxy-1,2-ethanediyl), α,α',α'',α'''-[(1R,2R,3R,5R)-5-carboxy-1,2,3,5-cyclohexanetetrayltetrakis(oxycarbonylimino-2,1-ethanediyl)]tetrakis[ω-methoxy-, ether with (1α,3R,4α,5R)-1,3,4,5-tetrakis[[[(2-hydroxyethyl)amino]carbonyl]oxy]cyclohexanecarboxylic acid (4:1) (9CI) (CA INDEX NAME)

Searched by: Mary Hale 571-272-2507 REM 1D86

PAGE 1-A

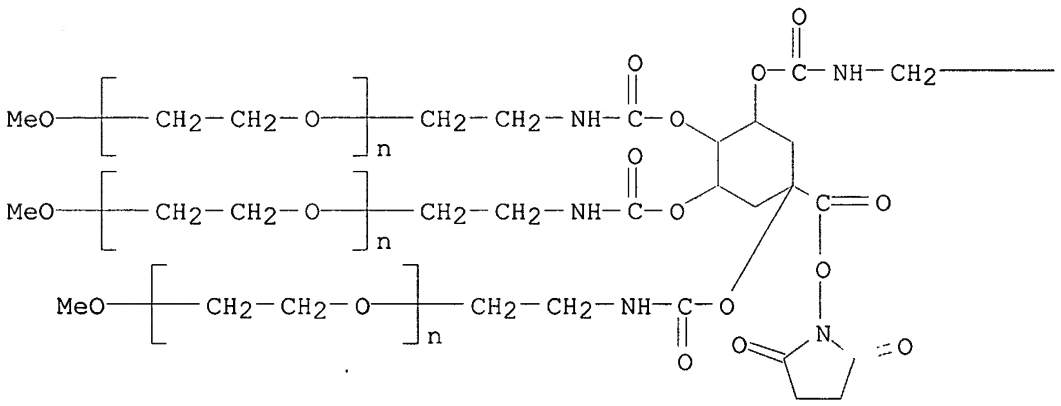


PAGE 1-B

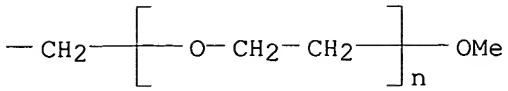


IT **479421-78-8DP**, conjugates with polypeptides
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of polyalkylene glycol derivative-modified biol. active polypeptides for ointments)
RN 479421-78-8 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α,α',α'',α'''-[[(1R,2α,3R,5α)-5-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]-1,2,3,5-cyclohexanetetrayl]tetrakis(oxycarbonylimino-2,1-ethanediyl)]tetrakis[ω-methoxy- (9CI) (CA INDEX NAME)

PAGE 1-A



Searched by: Mary Hale 571-272-2507 REM 1D86



L4 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
2002:594916 Document No. 137:159338 Branched polyalkylene glycols for modification of bioactive peptides. Yamasaki, Motoo; Suzawa, Toshiyuki; Murakami, Tatsuya; Sakurai, Noriko; Yamashita, Kinya; Mukai, Mayumi; Kuwabara, Takashi (Kyowa Hakko Kogyo Co., Ltd., Japan). PCT Int. Appl. WO 2002060978 A1 20020808, 82 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP709 20020130. PRIORITY: JP 2001-21616 20010130.

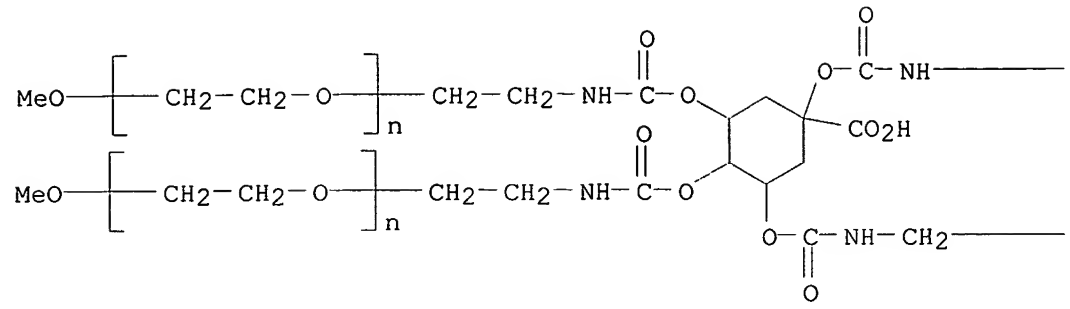
AB Disclosed are branched polyalkylene glycols which comprise at least three single-chain polyalkylene glycols bonded to each other and have a group reactive with an amino acid side chain, an N-terminal amino group or a C-terminal carboxyl group in a polypeptide or a group which can be converted into the reactive group as described above attached thereto; and physiol. active polypeptides modified by these branched polyalkylene glycols. A three single-chain branched polyethylene glycol derivative was prepared from tricine and Me(OC2H5)nNCO. The obtained PEG derivative was esterified with N-hydroxysuccinimide, and reacted with recombinant human interferon-β (rhIFN-β) solution The modified rhIFN-β showed improved antivirus activity in FL cells and blood IFN-β concentration in mice as compared with unmodified rhIFN-β.

IT **445389-29-7DP**, esters, reaction products with bioactive peptides
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(branched polyalkylene glycols for modification of bioactive peptides)

RN 445389-29-7 HCAPLUS

CN Poly(oxy-1,2-ethanediyl), α,α',α'',α'''-[(1R,2R,3R,5R)-5-carboxy-1,2,3,5-cyclohexanetetrayltetrakis(oxycarbonylimino-2,1-ethanediyl)]tetrakis[ω-methoxy-, ether with (1α,3R,4α,5R)-1,3,4,5-tetrakis[[[(2-hydroxyethyl)amino]carbonyl]oxy]cyclohexanecarboxylic acid (4:1) (9CI) (CA INDEX NAME)

PAGE 1-A



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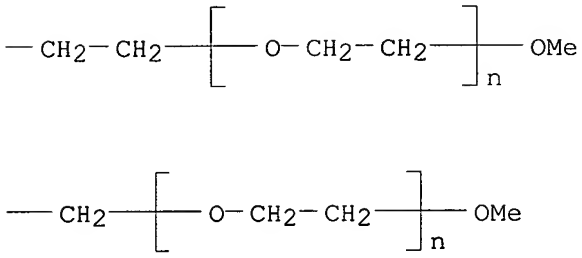


L4 ANSWER 4 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

2002:429732 Document No. 137:140706 Asymmetric Total Synthesis of 11-Deoxytetrodotoxin, a Naturally Occurring Congener. Nishikawa, Toshio; Asai, Masanori; Isobe, Minoru (Graduate School of Bioagricultural Sciences, Nagoya University, Chikusa Nagoya, 464-8601, Japan). Journal of the American Chemical Society, 124(26), 7847-7852 (English) 2002. CODEN: JACSAT. ISSN: 0002-7863. OTHER SOURCES: CASREACT 137:140706. Publisher: American Chemical Society.

AB Tetrodotoxin, a toxic principle of puffer fish poisoning, is a specific blocker of sodium channel. Despite many synthetic efforts since the structure elucidation in 1964, the only total synthesis of the racemic tetrodotoxin has been reported by Kishi and co-workers. In the course of our studies directed toward the total synthesis to analyze biol. interesting issues associated with tetrodotoxin, we accomplished a highly stereocontrolled synthesis of (-)-5,11-dideoxytetrodotoxin in 1999. Based on the synthesis, we describe herein the first total synthesis of 11-deoxytetrodotoxin, a naturally occurring analog. The synthesis started from an allylic alc., the same intermediate for the synthesis of 5,11-dideoxytetrodotoxin. Epoxidn. of the allylic alc. was followed by isomerization with Ti(i-PrO)4 to give an α-hydroxy allylic alc., in which the configurations of the two hydroxyl groups were inverted by oxidation and then a 2-step reduction Further epoxidn. of the allylic alc. and ozonolysis of the remaining vinyl group gave an aldehyde, which reacted with magnesium acetylide to give a propargyl alc. in a stereoselective manner. Oxidative cleavage of the acetylenic moiety with RuO4 afforded a fully functionalized lactone for 11-deoxytetrodotoxin. Crucial guanidinylation was achieved from trichloroacetamide according to our own method to give acetyldibenzylguanidine. Finally, deprotection of benzyl groups, acetates, and acetal furnished 11-deoxytetrodotoxin.

IT **444681-02-1P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

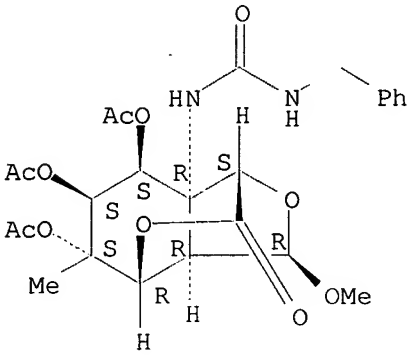
Searched by: Mary Hale 571-272-2507 REM 1D86

(asym. total synthesis of deoxytetrodotoxin, a naturally occurring congener)

RN 444681-02-1 HCAPLUS

CN Urea, N-(phenylmethyl)-N'-[(1S,3R,3aR,4R,5S,6S,7S,7aR)-5,6,7-tris(acetyloxy)hexahydro-3-methoxy-5-methyl-9-oxo-4,1-(epoxymethano)isobenzofuran-7a(1H)-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

2001:827032 Document No. 136:177464 QSAR of the inhibition of angiogenesis by TNP-470 and ovalicin analogues: another example of an allosteric interaction. Mekapati, Suresh Babu; Hansch, Corwin (Department of Chemistry, Pomona College, Claremont, CA, 91711, USA). Bioorganic & Medicinal Chemistry, 9(12), 3225-3230 (English) 2001. CODEN: BMECEP. ISSN: 0968-0896. Publisher: Elsevier Science Ltd..

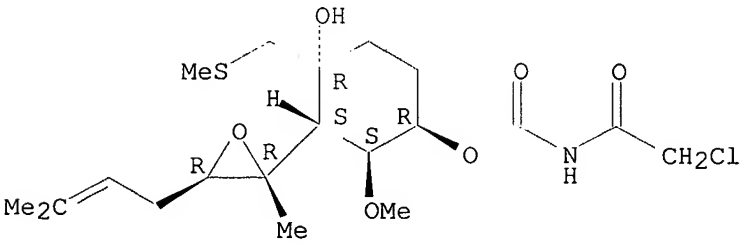
AB QSAR have been formulated for variations of TNP-470 and Ovalicin on various cell lines. In the examples of mouse lymphocyte cells and bovine endothelial cells the results suggest an allosteric interaction. These results are compared with the binding of nitrobenzene to Hb in rats in vivo. Such a reaction does not occur with methionine aminopeptidase.

IT **135149-58-5 214688-39-8**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(QSAR of TNP-470 and ovalicin analogs as angiogenesis inhibitors)

RN 135149-58-5 HCAPLUS

CN Carbamic acid, (chloroacetyl)-, (1R,2S,3S,4R)-4-hydroxy-2-methoxy-3-[(2R,3R)-2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-4-[(methylthio)methyl]cyclohexyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



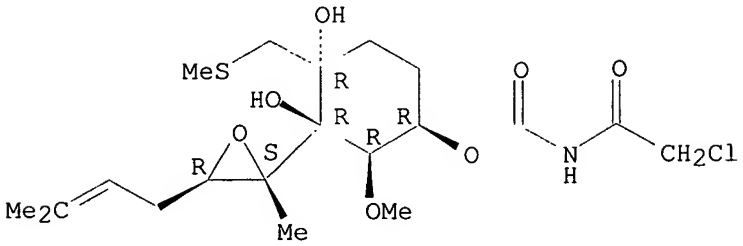
RN 214688-39-8 HCAPLUS

CN Carbamic acid, (chloroacetyl)-, (1R,2R,3R,4R)-3,4-dihydroxy-2-methoxy-3-[(2S,3R)-2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-4-

Searched by: Mary Hale 571-272-2507 REM 1D86

[(methylthio)methyl]cyclohexyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



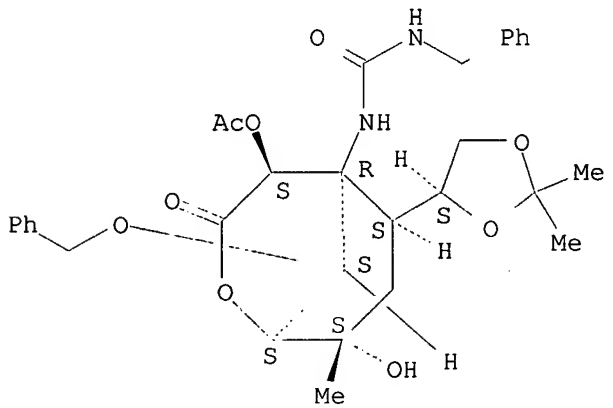
L4 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
2001:351827 Document No. 135:153041 Stereocontrolled synthesis of (-)-5,11-dideoxytetrodotoxin. Asai, M.; Nishikawa, T.; Ohyabu, N.; Yamamoto, N.; Isobe, M. (School of Bioagricultural Sciences, Laboratory of Organic Chemistry, Nagoya University, Chikusa, Nagoya, 464-8601, Japan). Tetrahedron, 57(21), 4543-4558 (English) 2001. CODEN: TETRAB. ISSN: 0040-4020. OTHER SOURCES: CASREACT 135:153041. Publisher: Elsevier Science Ltd..

AB Asym. synthesis of (-)-5,11-dideoxytetrodotoxin, an analog of puffer fish toxin, was accomplished from a common key intermediate through a novel hydroxylation at the C-8 position with neighboring group participation of trichloroacetamide, a highly stereoselective addition of acetylide as an equivalent of carboxylic acid, and a new guanidine synthesis from trichloroacetamide as key steps. This study presents the first asym. synthesis among tetrodotoxin and its analogs.

IT **253674-47-4P 253674-50-9P 352670-29-2P 352670-33-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stereocontrolled synthesis of dideoxytetrodotoxin via hydroxylation stereoselective addition of acetylide and guanidine)

RN 253674-47-4 HCAPLUS
CN Urea, N-[(1S,4S,5R,6S,8S,9S)-4-(acetyloxy)-6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-8-hydroxy-8-methyl-3-oxo-9-(phenylmethoxy)-2-oxabicyclo[3.3.1]non-5-yl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

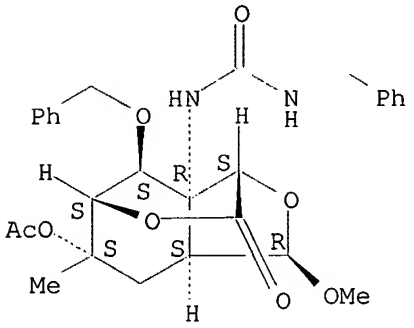


RN 253674-50-9 HCAPLUS

Searched by: Mary Hale 571-272-2507 REM 1D86

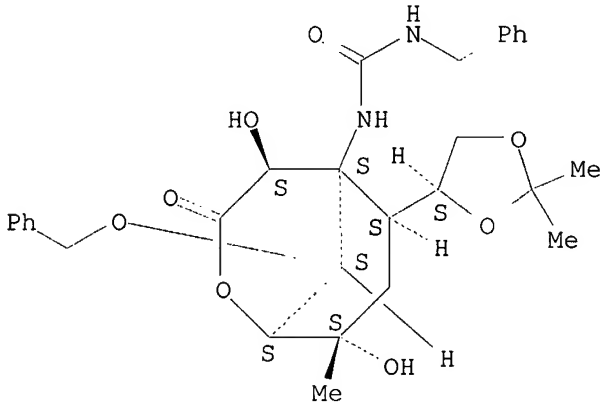
CN Urea, N-[(2R,3S,3aR,4S,5S,7aS,8S)-8-(acetyloxy)hexahydro-2-methoxy-8-methyl-7-oxo-4-(phenylmethoxy)-3,5-ethano-3aH-furo[2,3-c]pyran-3a-yl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 352670-29-2 HCAPLUS
CN Urea, N-[(1S,4S,5S,6S,8S,9S)-6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-4,8-dihydroxy-8-methyl-3-oxo-9-(phenylmethoxy)-2-oxabicyclo[3.3.1]non-5-yl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

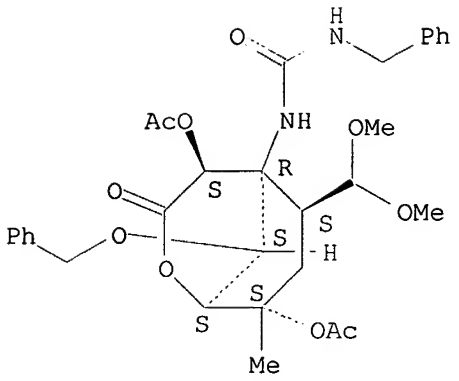
Absolute stereochemistry.



RN 352670-33-8 HCAPLUS
CN Urea, N-[(1S,4S,5R,6S,8S,9S)-4,8-bis(acetyloxy)-6-(dimethoxymethyl)-8-methyl-3-oxo-9-(phenylmethoxy)-2-oxabicyclo[3.3.1]non-5-yl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

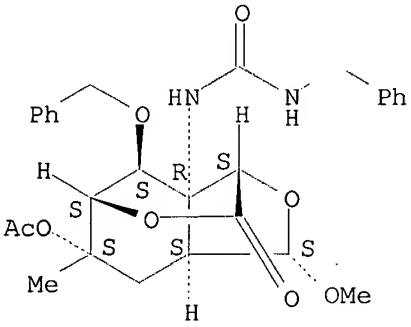
Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



IT **352670-36-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(stereocontrolled synthesis of dideoxytetrodotoxin via hydroxylation stereoselective addition of acetylide and guanidine)
RN 352670-36-1 HCAPLUS
CN Urea, N-[(2S,3S,3aR,4S,5S,7aS,8S)-8-(acetyloxy)hexahydro-2-methoxy-8-methyl-7-oxo-4-(phenylmethoxy)-3,5-ethano-3aH-furo[2,3-c]pyran-3a-yl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L4 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
1999:776263 Document No. 133:4873 Synthetic studies on optically active tetrodotoxin analogs. Asai, Masanori; Nishikawa, Toshio; Ohyabu, Norio; Yamamoto, Noboru; Isobe, Minoru (Graduate School of Bioagricultural Sciences, Nagoya University, Japan). Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 41st, 7-12 (Japanese) 1999. CODEN: TYKYDS. Publisher: Nippon Kagakkai.
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Tetrodotoxin (TTX) is a well-known marine natural product acting as toxic principle of puffer fish poisoning and has been used as a specific blocker of Na-channel proteins. However, the biosynthesis, the mechanisms of bioaccumulation, the details of bound structure to Na-channel protein, etc., are remained to uncover. In order to solve such problems under mol. level, the authors have studied syntheses of TTX and its analogs as

Searched by: Mary Hale 571-272-2507 REM 1D86

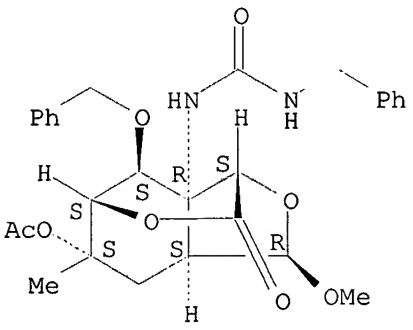
enantiomerically pure form. Herein the authors present a highly stereocontrolled synthesis of (-)-5,11-dideoxyTTX (I). The synthesis started from the Diels-Alder reaction between bromolevoglucosenone (II) derived from levoglucosenone as a chiral starting material and isoprene to construct cyclohexane ring (III), which was transformed to exo-allylic alc. (IV) in 5 steps. The amino functionality was introduced by the Overman rearrangement of IV to give trichloroacetamide (V) which has all of the carbon atoms of TTX skeleton. Hydroxylation at C-8 position of the key intermediate V was achieved using a neighboring group participation of the trichloroacetamide. Inversion of the resulting hydroxy group, stereoselective epoxidn. and ozonolysis of the vinyl group yielded an aldehyde (VI). Stereoselective addition of magnesium acetylide to the aldehyde VI, followed by oxidative cleavage of the acetylene group with RuO,4 gave the lactone (VII). Construction of guanidine function from trichloroacetamide of VII by the authors' new procedure resulted in failure because of the labile C-9 acetoxy group. In order to avoid such problems, the authors considered an urea compound (VIII; R = NHCONHBn) as a candidate of precursor for guanyl formation. The urea VIII (R = NHCONHBn) was dehydrated to carbodiimide VIII (R = N:C:NBn), which reacted with benzylamine to afford dibenzylguanidine VIII [R = NHC(:NBn)NHBn]. Finally deprotection of benzyl groups, acetyl groups and acetal furnished the 5,11-dideoxyTTX (I) along with its isomers. This studies presents the first asym. synthesis of TTX analogs and provides a practical route accessible to the labeled compds. for biochem. studies. Further studies toward naturally occurring TTX and other analogs are in progress in the laboratory

IT **253674-50-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthetic studies on optically active tetrodotoxin analogs)

RN 253674-50-9 HCAPLUS

CN Urea, N-[(2R,3S,3aR,4S,5S,7aS,8S)-8-(acetyloxy)hexahydro-2-methoxy-8-methyl-7-oxo-4-(phenylmethoxy)-3,5-ethano-3aH-furo[2,3-c]pyran-3a-yl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

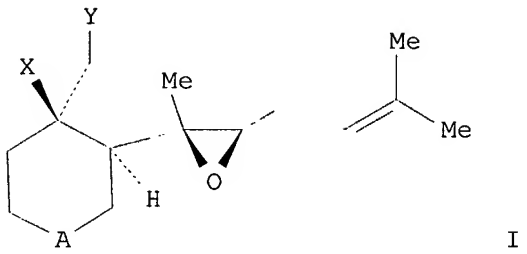


L4 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

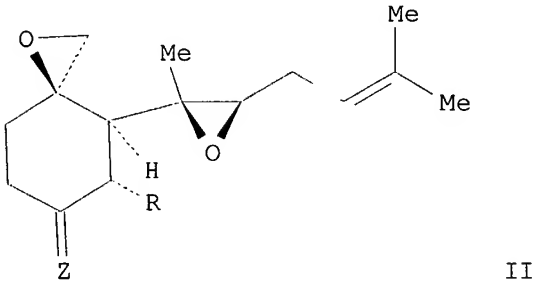
1999:753227 Document No. 132:3480 Preparation of 5-demethoxyfumagillol derivatives as angiogenesis inhibitors. Hong, Chung Il; Kim, Jung Woo; Lee, Sang Joon; Ahn, Soon Kil; Choi, Nam Song; Hong, Ryung Kee; Chun, Hyoung Sik; Moon, Seung Kee; Lee, Hong Woo (Chong Kun Dang Corporation, S. Korea). PCT Int. Appl. WO 9959987 A1 19991125, 34 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN,

YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-KR230 19990511. PRIORITY: KR 1998-17637 19980515.

GI



I



II

AB The title compds. [I; A = CH(OH), CH(NH2), CO, CHOCOR3, etc.; X = OH; Y = halo, (S+R1R2, Z-); R1, R2 = H, (un)substituted alkyl; Z- = counter ion; provided that R1 and R2 do not represent H at the same time; or XY may form an oxirane ring], useful as excellent angiogenesis inhibiting agents, are prepared; also, II [R = α-MeO, Z = O] was demethoxylated to give II [R = H, Z = O], which was then reduced to give II [R = H, Z = (α-OH, β-H)] (5-demethoxyfumagillol). Thus, 5-demethoxyfumagillin, obtained from fermentation broth of Aspergillus fumigatus, was stirred with 0.1 N NaOH at room temperature for 6 h to give 5-demethoxyfumagillol. Also, SmI2 was added to ketone II [R = MeO, Z = O] in THF-MeOH at 78° over 30 min and the resulting mixture was stirred at room temperature for 30 min to give II [R = H, Z = O], which was reduced with NaBH4 in MeOH to give II [R = H, Z = (α-OH, β-H)]. This was reacted with chloroacetyl isocyanate in CH2Cl2 containing (dimethylamino)pyridine to give 5-demethoxy-6-O-(chloroacetylcarbamoyl)fumagillol (III). In an in vitro study measuring the angiogenesis inhibiting activity by means of MTT method using calf pulmonary artery endothelial cells, III had an IC50 of 2.8+10-4 g/mL vs. 3.2+10-3 g/mL for fumagillin. Pharmaceutical compns. containing I are described.

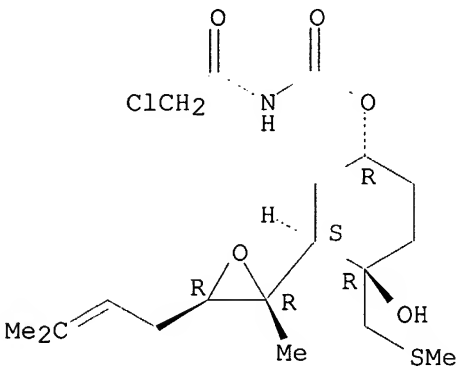
IT **251116-28-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of 5-demethoxyfumagillol derivs. as angiogenesis inhibitors)

RN 251116-28-6 HCAPLUS

CN Carbamic acid, (chloroacetyl)-, (1R,3S,4R)-4-hydroxy-3-[(2R,3R)-2-methyl-3-

(3-methyl-2-butenyl)oxiranyl]-4-[(methylthio)methyl]cyclohexyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

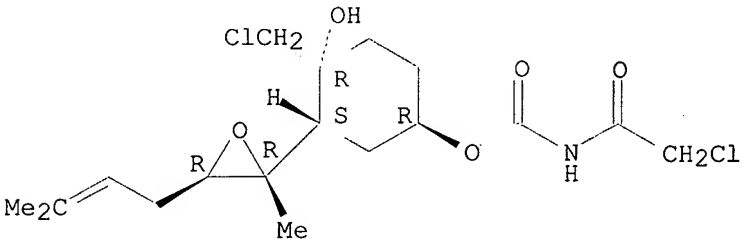


IT **251116-20-8P 251116-29-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 5-demethoxyfumagillol derivs. as angiogenesis inhibitors)

RN 251116-20-8 HCAPLUS

CN Carbamic acid, (chloroacetyl)-, (1R,3S,4R)-4-(chloromethyl)-4-hydroxy-3-[(2R,3R)-2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl ester (9CI) (CA INDEX NAME)

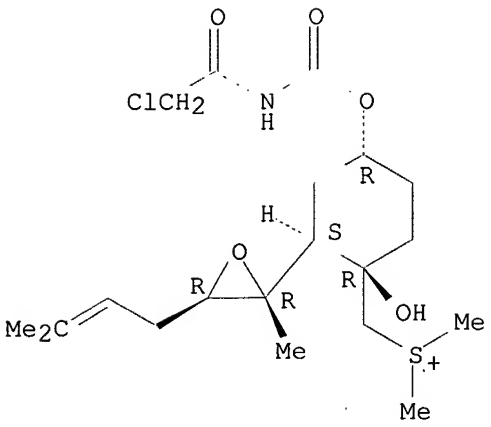
Absolute stereochemistry.



RN 251116-29-7 HCAPLUS

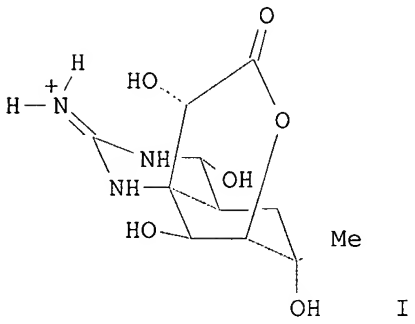
CN Sulfonium, [[(1R,2S,4R)-4-[[[(chloroacetyl)amino]carbonyl]oxy]-1-hydroxy-2-[(2R,3R)-2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl]methyl]dimethyl-, iodide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● I^-

L4 ANSWER 9 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
1999:701963 Document No. 132:78781 Stereocontrolled synthesis of (-)-5,11-dideoxytetrodotoxin. Nishikawa, Toshio; Asai, Masanori; Ohyabu, Norio; Yamamoto, Noboru; Isobe, Minoru (Laboratory of Organic Chemistry School of Bioagricultural Sciences, Nagoya University, Nagoya, 464-8601, Japan). Angewandte Chemie, International Edition, 38(20), 3081-3084 (English) 1999. CODEN: ACIEF5. ISSN: 1433-7851. OTHER SOURCES: CASREACT 132:78781. Publisher: Wiley-VCH Verlag GmbH.
GI

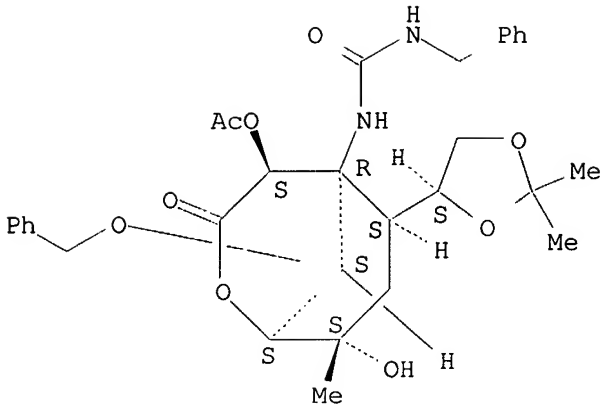


I

AB Stereocontrolled synthesis of (-)-5,11-dideoxytetrodotoxin I via stereoselective hydride reduction, is reported.
IT **253674-47-4P 253674-50-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stereocontrolled synthesis of dideoxytetrodotoxin via stereoselective hydride reduction)
RN 253674-47-4 HCAPLUS
CN Urea, N-[(1S,4S,5R,6S,8S,9S)-4-(acetyloxy)-6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-8-hydroxy-8-methyl-3-oxo-9-(phenylmethoxy)-2-oxabicyclo[3.3.1]non-5-yl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

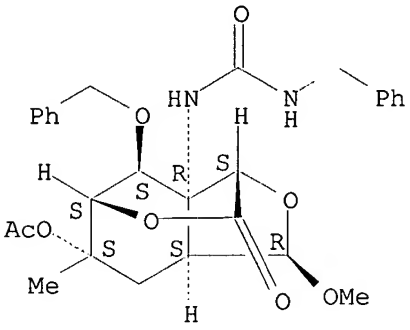
Absolute stereochemistry. Rotation (-).

Searched by: Mary Hale 571-272-2507 REM 1D86



RN 253674-50-9 HCAPLUS
CN Urea, N-[(2R,3S,3aR,4S,5S,7aS,8S)-8-(acetyloxy)hexahydro-2-methoxy-8-methyl-7-oxo-4-(phenylmethoxy)-3,5-ethano-3aH-furo[2,3-c]pyran-3a-yl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

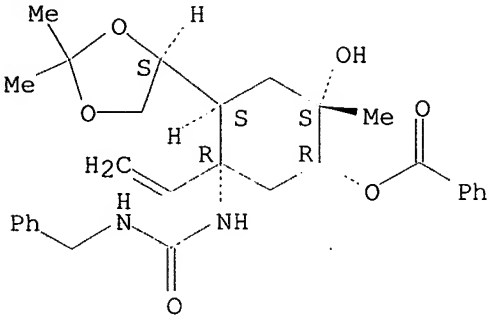
Absolute stereochemistry. Rotation (-).



L4 ANSWER 10 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
1999:256010 Document No. 130:282278 New synthetic route of guanidine from trichloroacetamide for tetrodotoxin and its related compounds. Nishikawa, Toshio; Ohyabu, Norio; Yamamoto, Noboru; Isobe, Minoru (Laboratory of Organic Chemistry, School of Bioagricultural Sciences, Nagoya University, Nagoya, 464-8601, Japan). Tetrahedron, 55(14), 4325-4340 (English) 1999. CODEN: TETRAB. ISSN: 0040-4020. Publisher: Elsevier Science Ltd..
AB Trichloroacetamide was transformed into dibenzylguanidinium salt in three steps. Attempted debenzylation was very difficult in the guanidinium form even under high pressure hydrogen and high temperature conditions. On the other hand, the benzyl groups on acetylated guanidine were easily deprotected by hydrogenolysis under 1 atm of hydrogen. These methods were applied to the syntheses of tetrodotoxin-related compds.
IT **222983-17-7P 222983-18-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(new synthetic route of guanidine from trichloroacetamide for tetrodotoxin and its related compds.)
RN 222983-17-7 HCAPLUS
CN Urea, N-[(1R,2S,4S,5R)-5-(benzoyloxy)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-ethenyl-4-hydroxy-4-methylcyclohexyl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

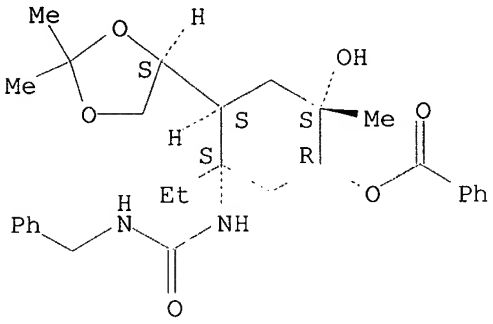
Searched by: Mary Hale 571-272-2507 REM 1D86

Absolute stereochemistry. Rotation (+).



RN 222983-18-8 HCAPLUS
CN Urea, N-[(1S,2S,4S,5R)-5-(benzoyloxy)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-ethyl-4-hydroxy-4-methylcyclohexyl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 11 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
1999:7815 Document No. 130:76195 Type 2 methionine aminopeptidase (MetAP2) inhibitors and uses thereof. Liu, Jun O.; Griffith, Eric C.; Su, Zhuang (Massachusetts Institute of Technology, USA). PCT Int. Appl. WO 9856372 A1 19981217, 99 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US11775 19980608. PRIORITY: US 1997-49159 19970609.

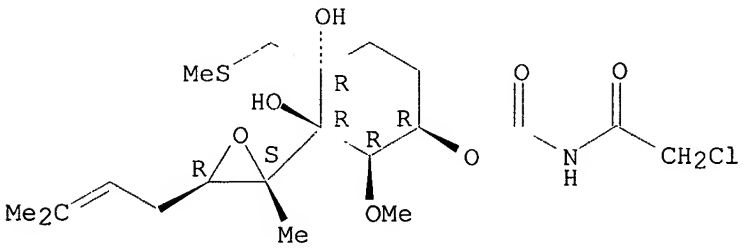
AB Compds. that are anti-angiogenic or immunosuppressive are described. Also described are methods for determining if an animal is at risk for a disease involving abnormal angiogenesis or an immune reaction resulting in pathol. comprising evaluating an aspect of MetAP2 metabolism or structure; methods for identifying agents that are anti-angiogenic or immunosuppressive comprising evaluating the effect of the agent on an aspect of MetAP2 metabolism; methods for treating a cell having an abnormality in metabolism or structure of MetAP2; and methods for treating abnormal angiogenesis or an immune reaction which results in pathol. in an animal. Pharmaceutical compns. are also provided.

IT **214688-39-8P**, FOS 67
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(methionine aminopeptidase type 2 inhibitors, preparation, pharmaceuticals, and therapeutic and diagnostic uses)
RN 214688-39-8 HCAPLUS

Searched by: Mary Hale 571-272-2507 REM 1D86

CN Carbamic acid, (chloroacetyl)-, (1R,2R,3R,4R)-3,4-dihydroxy-2-methoxy-3-[(2S,3R)-2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-4-[(methylthio)methyl]cyclohexyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

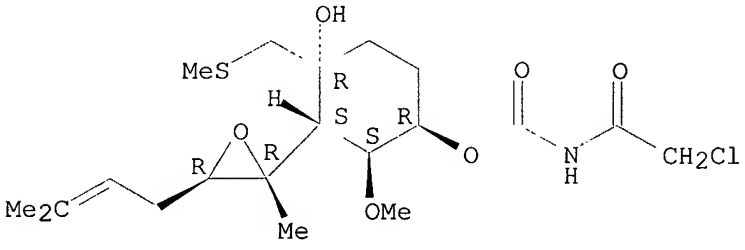


IT **135149-58-5**, FOS 64
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methionine aminopeptidase type 2 inhibitors, preparation, pharmaceuticals, and therapeutic and diagnostic uses)

RN 135149-58-5 HCAPLUS

CN Carbamic acid, (chloroacetyl)-, (1R,2S,3S,4R)-4-hydroxy-2-methoxy-3-[(2R,3R)-2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-4-[(methylthio)methyl]cyclohexyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

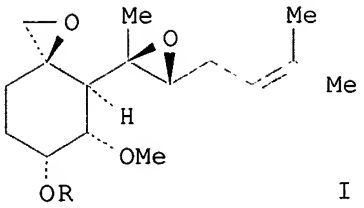


L4 ANSWER 12 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

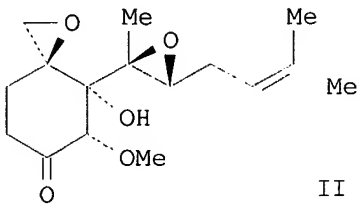
1998:617871 Document No. 129:316388 Synthetic analogs of TNP-470 and ovalicin reveal a common molecular basis for inhibition of angiogenesis and immunosuppression. Turk, Benjamin E.; Su, Zhuang; Liu, Jun O. (Center for Cancer Research and Departments of Biology and Chemistry, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA). Bioorganic & Medicinal Chemistry, 6(8), 1163-1169 (English) 1998. CODEN: BMECEP. ISSN: 0968-0896. Publisher: Elsevier Science Ltd..

GI

Searched by: Mary Hale 571-272-2507 REM 1D86



I



II

AB TNP-470 (I; R = NHCOCH2Cl), a synthetic derivative of the natural product fumagillin [I; R = (CH:CH)5CO2H-trans-all], potently inhibits angiogenesis in vivo and the growth of endothelial cell cultures in vitro. The structurally related natural product ovalicin (II) also inhibits angiogenesis but possesses potent immunosuppressive activity. The recent finding that all three drugs bind and inhibit the same target, methionine aminopeptidase 2 (MetAP2), raised the question of whether TNP-470 is also immunosuppressive and whether inhibition of MetAP2 underlies both activities of ovalicin. To address these questions, we synthesized a series of analogs of TNP-470 and ovalicin and tested them for their abilities to inhibit the proliferation of either endothelial cell or mixed lymphocyte cultures. TNP-470 and its analogs were found to possess both immunosuppressive and anti-angiogenic activities. A strong correlation was observed between the ability of compds. to inhibit bovine and human endothelial cell growth and their ability to inhibit the mouse mixed lymphocyte reaction (MLR), implying that the two activities share a common mol. basis, i.e., inhibition of MetAP2. Interestingly, ovalicin and several other compds. behaved differently in the human MLR than in either the mouse MLR or human endothelial cell proliferation assays, pointing to possible species-specific and cell type-specific differences in the metabolism or uptake of these compds.

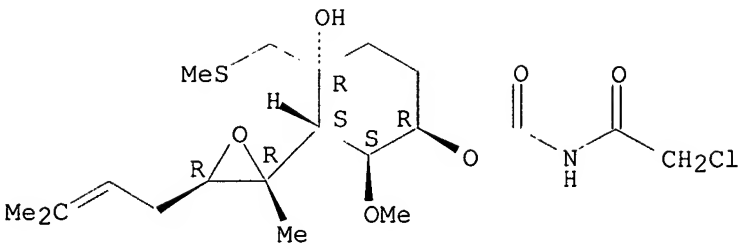
IT **135149-58-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of TNP-470 and ovalicin analogs with a common mol. basis for inhibition of angiogenesis and immunosuppression)

RN 135149-58-5 HCAPLUS

CN Carbamic acid, (chloroacetyl)-, (1R,2S,3S,4R)-4-hydroxy-2-methoxy-3-[(2R,3R)-2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-4-[(methylthio)methyl]cyclohexyl ester (9CI) (CA INDEX NAME)

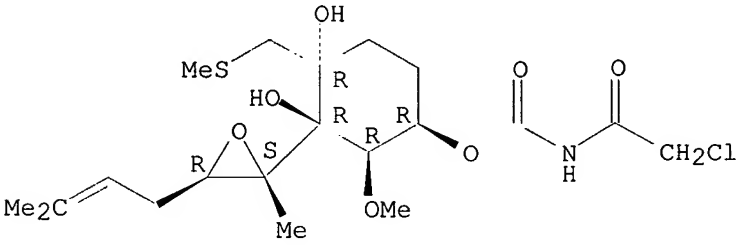
Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



IT **214688-39-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of TNP-470 and ovalicin analogs with a common mol. basis for inhibition of angiogenesis and immunosuppression)
RN 214688-39-8 HCAPLUS
CN Carbamic acid, (chloroacetyl)-, (1R,2R,3R,4R)-3,4-dihydroxy-2-methoxy-3-[(2S,3R)-2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-4-[(methylthio)methyl]cyclohexyl ester (9CI) (CA INDEX NAME)

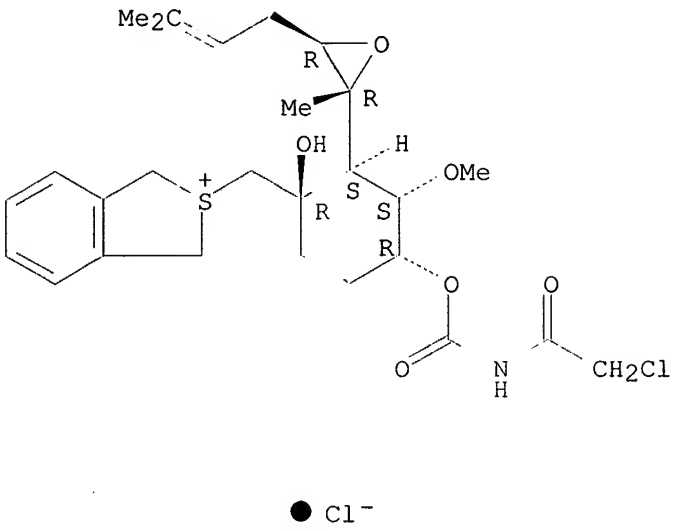
Absolute stereochemistry.



L4 ANSWER 13 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
1997:678882 Document No. 127:336644 Oral composition comprising a fumagillol derivative. Yanai, Shigeo; Sudo, Katsuichi; Akiyama, Yohko; Nagahara, Naoki (Takeda Chemical Industries, Ltd., Japan). Eur. Pat. Appl. EP 799616 A1 19971008, 18 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI. (English). CODEN: EPXXDW. APPLICATION: EP 1997-105186 19970327. PRIORITY: JP 1996-78896 19960401; JP 1996-159654 19960620; JP 1996-187387 19960717.
AB The present invention relates to a pharmaceutical composition for oral administration in which a fumagillol derivative is stabilized and exhibits remarkable antiangiogenesis activity in oral administration. 6-O-(N-chloroacetylcarbamoyl)fugmagillol was dissolved in Miglyol 812 at a final concentration of 100 mg/mL and capsules were filled with the obtained homogeneous solution, then the capsules were coated with hydroxypropyl Me cellulose phthalate to provide an enteric capsule.
IT **135150-27-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. containing fumagillol derivs.)
RN 135150-27-5 HCAPLUS
CN Benzo[c]thiophenium, 2-[[4-[[[(chloroacetyl)amino]carbonyl]oxy]-1-hydroxy-3-methoxy-2-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl]methyl]-1,3-dihydro-, chloride, [1R-[1α,2α(2R*,3R*),3β,4β]]- (9CI) (CA INDEX NAME)

Searched by: Mary Hale 571-272-2507 REM 1D86

Absolute stereochemistry.



L4 ANSWER 14 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

1997:468344 Document No. 127:214666 Methionine aminopeptidase (type 2) is the common target for angiogenesis inhibitors AGM-1470 and ovalicin. Griffith, Eric C.; Su, Zhuang; Turk, Benjamin E.; Chen, Shaoping; Chang, Yie-Hwa; Wu, Zhuchun; Biemann, Klaus; Liu, Jun O. (Cent. for Cancer Res., Massachusetts Inst. of Technol., Cambridge, MA, 02139, USA). Chemistry & Biology, 4(6), 461-471 (English) 1997. CODEN: CBOLE2. ISSN: 1074-5521. Publisher: Current Biology.

AB Angiogenesis, the formation of new blood vessels, is essential for tumor growth. The inhibition of angiogenesis is therefore emerging as a promising therapy for cancer. Two natural products, fumagillin and ovalicin, were discovered to be potent inhibitors of angiogenesis due to their inhibition of endothelial cell proliferation. An analog of fumagillin, AGM-1470, is currently undergoing clin. trials for the treatment of a variety of cancers. The underlying mol. mechanism of the inhibition of angiogenesis by these natural drugs has remained unknown. Both AGM-1470 and ovalicin bind to a common bifunctional protein, identified by mass spectrometry as the type 2 methionine aminopeptidase (MetAP2). This protein also acts as an inhibitor of eukaryotic initiation factor 2α (eIF-2α) phosphorylation. Both drugs potently inhibit the methionine aminopeptidase activity of MetAP2 without affecting its ability to block eIF-2α phosphorylation. There are two types of methionine aminopeptidase found in eukaryotes, but only the type 2 enzyme is inhibited by the drugs. A series of analogs of fumagillin and ovalicin were synthesized and their potency for inhibition of endothelial cell proliferation and inhibition of methionine aminopeptidase activity was determined A significant correlation was found between the two activities. The protein MetAP2 is a common mol. target for both AGM-1470 and ovalicin. This finding suggests that MetAP2 may play a critical role in the proliferation of endothelial cells and may serve as a promising target for the development of new anti-angiogenic drugs.

IT **194092-20-1 194092-26-7**

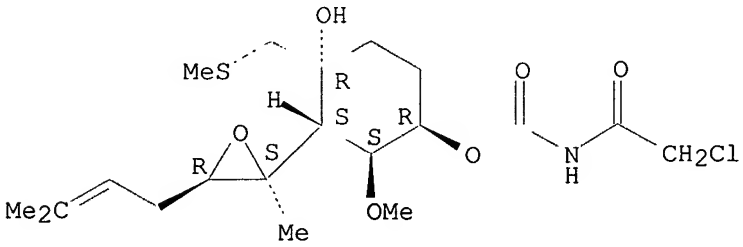
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(methionine aminopeptidase (type 2) is the common target for angiogenesis inhibitors AGM-1470 and ovalicin)

Searched by: Mary Hale 571-272-2507 REM 1D86

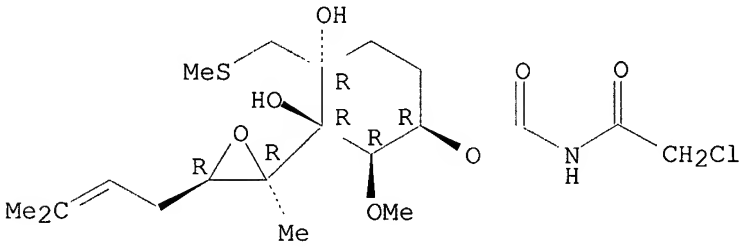
RN 194092-20-1 HCAPLUS
CN Carbamic acid, (chloroacetyl)-, 4-hydroxy-2-methoxy-3-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-4-[(methylthio)methyl]cyclohexyl ester, [1R-[1α,2α,3β(2S*,3R*),4β]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

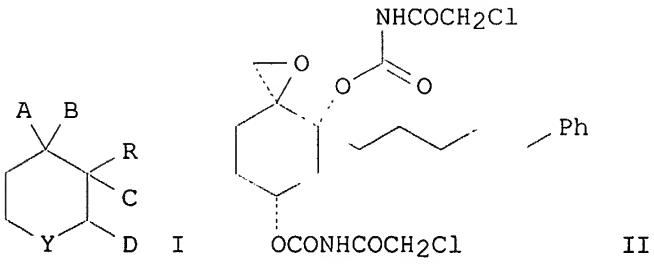


RN 194092-26-7 HCAPLUS
CN Carbamic acid, (chloroacetyl)-, 3,4-dihydroxy-2-methoxy-3-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-4-[(methylthio)methyl]cyclohexyl ester, [1R-[1α,2α,3α,3(2R*,3R*),4β]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 15 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
1996:740268 Document No. 126:7974 Preparation and formulation of oxaspirooctane derivatives as antitumor agents. Billington, David C.; Picard, Isabelle; Atassi, Ghanem; Pierre, Alain; Burbridge, Michael; Guilbaud, Nicolas (Adir Et Compagnie, Fr.). Eur. Pat. Appl. EP 739887 A1 19961030, 51 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE. (French). CODEN: EPXXDW. APPLICATION: EP 1996-400872 19960424. PRIORITY: FR 1995-5052 19950427.
GI



I II

Searched by: Mary Hale 571-272-2507 REM 1D86

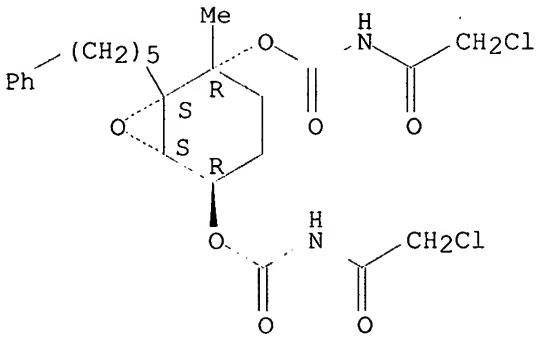
AB The title compds. I [R = C.tplbond.CR3, etc.; several definitions are given for A and B : for example, A = Me, and B = OR1; several definitions are given for C and D : for example, C = hydroxy, and D = H, Br; Y = CO, etc.; R1 = CONHCOR4; R3 = H, (un)substituted alkyl, etc.; R4 = (un)substituted alkyl, etc.] are prepared I are antitumor agents with angiogenesis inhibiting activity. The title compound II (preparation given) at 30 mg/Kg gave 56% inhibition of tumors in mice.

IT **183597-02-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of oxaspirooctane derivs. as antitumor agents)

RN 183597-02-6 HCAPLUS

CN Carbamic acid, (chloroacetyl)-, 2-methyl-1-(5-phenylpentyl)-7-oxabicyclo[4.1.0]heptane-2,5-diyl ester, (1α,2β,5α,6.alpha.)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 16 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

1995:741468 Document No. 123:314182 Chemical modification of fumagillin. III. Modification of the spiro-epoxide. Marui, Shogo; Yamamoto, Toshihiro; Sudo, Katsuichi; Akimoto, Hiroshi; Kishimoto, Shoji (Pharmaceutical Research Laboratories III, Takeda Chemical Industries, Osaka, 532, Japan). Chemical & Pharmaceutical Bulletin, 43(4), 588-93 (English) 1995. CODEN: CPBTAL. ISSN: 0009-2363. Publisher: Pharmaceutical Society of Japan.

AB The spiro-epoxy group of fumagillol was selectively modified and several analogs of AGM-1470 with a (dialkyl)-β-hydroxyethylsulfonium moiety were prepared These analogs were found to inhibit angiogenesis induced by basic fibroblast growth factor in the rat micropocket assay. They also inhibited the growth of M5076 cells in vivo, but did not affect the body weight change of the tested mice during the assay.

IT **135149-59-6P 135150-27-5P 135150-44-6P**
170080-68-9P 170080-69-0P 170080-70-3P
170080-71-4P 170080-72-5P 170080-73-6P
170080-74-7P 170080-75-8P 171964-50-4P
171964-60-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of fumagillin derivs.)

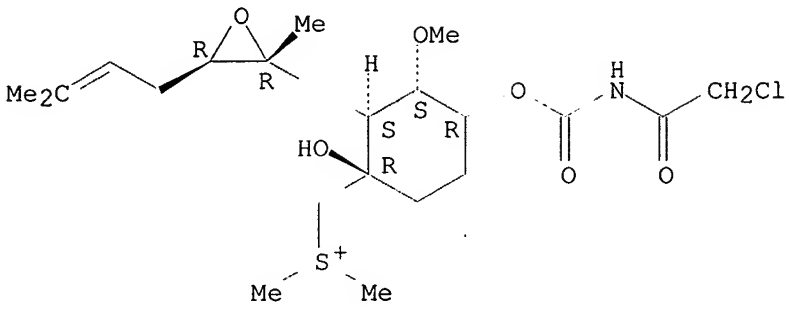
RN 135149-59-6 HCAPLUS

CN Sulfonium, [[4-[[[(chloroacetyl)amino]carbonyl]oxy]-1-hydroxy-3-methoxy-2-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl]methyl]dimethyl-, iodide, [1R-[1α,2α(2R*,3R*),3β,4β]]- (9CI) (CA

Searched by: Mary Hale 571-272-2507 REM 1D86

INDEX NAME)

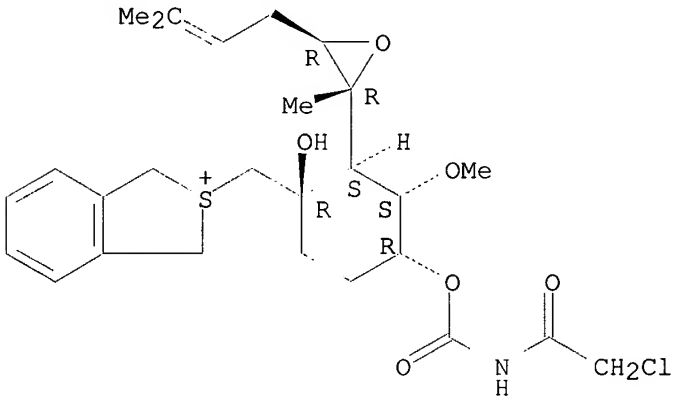
Absolute stereochemistry.



● I^-

RN 135150-27-5 HCAPLUS
CN Benzo[c]thiophenium, 2-[[4-[[[(chloroacetyl)amino]carbonyl]oxy]-1-hydroxy-3-methoxy-2-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl]methyl]-1,3-dihydro-, chloride, [1R-[1α,2α(2R*,3R*),3β,4β]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

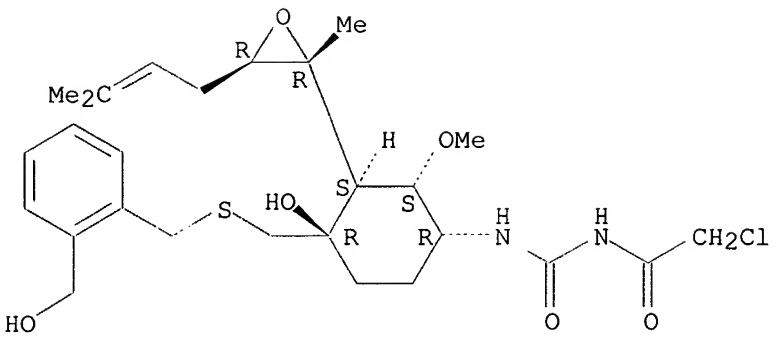


● Cl^-

RN 135150-44-6 HCAPLUS
CN Benzo[c]thiophenium, 2-[[4-[[[(chloroacetyl)amino]carbonyl]amino]-1-hydroxy-3-methoxy-2-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl]methyl]-1,3-dihydro-, chloride, [1R-[1α,2α(2R*,3R*),3β,4.beta.]]- (9CI) (CA INDEX NAME)

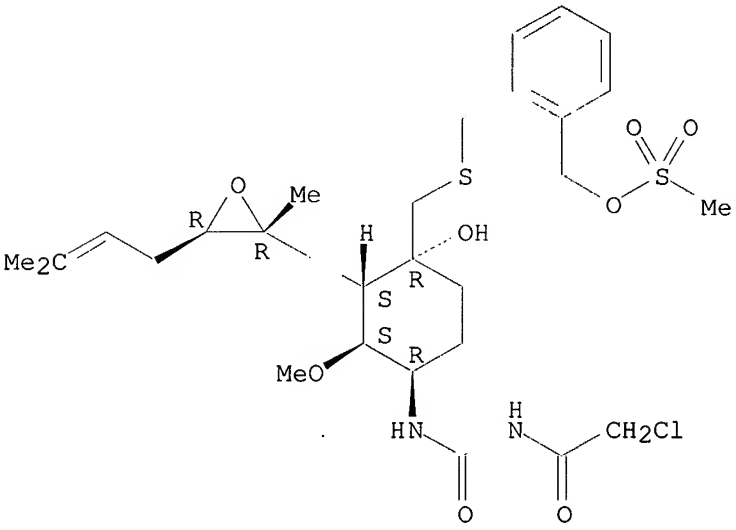
Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



RN 135150-43-5 HCAPLUS
CN Acetamide, 2-chloro-N-[[[4-hydroxy-2-methoxy-3-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-4-[[[[2-[[(methylsulfonyl)oxy]methyl]phenyl]methyl]thio]methyl]cyclohexyl]amino]carbonyl]-, [1R-[1α,2α,3β(2R*,3R*),4β]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

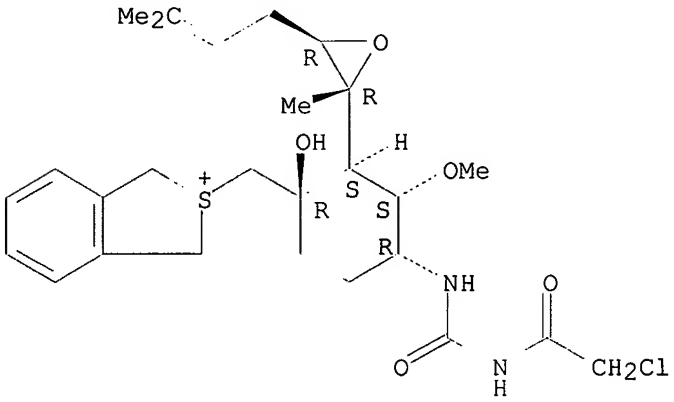


L4 ANSWER 17 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
1994:541680 Document No. 121:141680 Stable pharmaceutical composition of fumagillol derivatives. Yanai, Shigeo; Saito, Kazuhiro; Okada, Hiroaki (Takeda Chemical Industries, Ltd., Japan). Eur. Pat. Appl. EP 602586 A2 19940622, 15 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1993-120104 19931214. PRIORITY: JP 1992-335828 19921216.
AB A pharmaceutical composition having improved stability which comprises a fumagillol derivative and a fatty acid ester of glycerin or polyglycerin is disclosed. The composition is useful for treating diseases associated with angiogenesis such as hepatoma, etc. A solution of 10mg/mL 6-O-(N-chloroacetylcarbamoyl)fumagillol in Miglyol 812 which was stored under N at 37° for 14 days did not decomposed and was stable.
IT **135150-44-6**
RL: BIOL (Biological study)
(pharmaceutical compns. containing fatty acid ester of glycerin or polyglycerin and, stable)

Searched by: Mary Hale 571-272-2507 REM 1D86

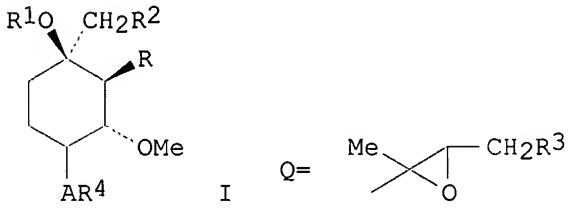
RN 135150-44-6 HCAPLUS
CN Benzo[c]thiophenium, 2-[[4-[[[(chloroacetyl)amino]carbonyl]amino]-1-hydroxy-3-methoxy-2-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl]methyl]-1,3-dihydro-, chloride, [1R-[1α,2α(2R*,3R*),3β,4.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● Cl^-

L4 ANSWER 18 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
1992:255844 Document No. 116:255844 Preparation of cyclodextrin complexes of fumagillols as antitumor agents. Kamei, Shigeru; Okada, Hiroaki; Sudo, Katsuichi; Kishimoto, Shoji (Takeda Chemical Industries, Ltd., Japan). Eur. Pat. Appl. EP 461427 A2 19911218, 17 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1991-108225 19910522. PRIORITY: JP 1990-136343 19900525; JP 1991-15333 19910206.
GI



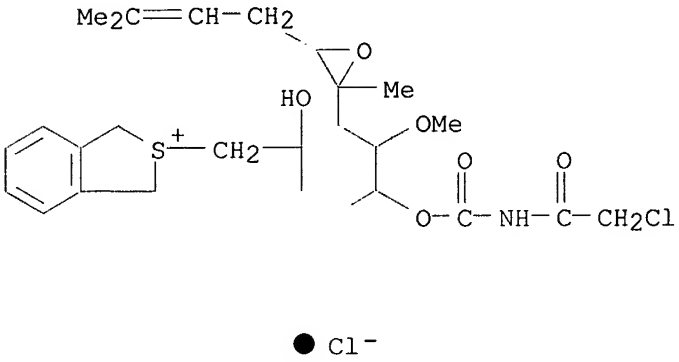
AB Complexes of fumagillols I (A = O, NR8; R = oxiranyl group Q; R1 = H; R2 = halo, NR5R6, SR5, etc.; R1R2 = bond; R3 = CH:CMe2, CH2CHMe2; R4 = H, hydrocarbyl, acyl, etc.; R5, R6 = hydrocarbyl, heterocyclyl; NR5R6 = heterocyclyl; R8 = H, alkyl, aryl, etc.) with (etherified) cyclodextrins, having enhanced aqueous solubility, were prepared Thus, 6-O-(N-chloroacetylcarbamoyl)fumagillol gave 72% growth-inhibition of mouse reticulum cell sarcoma M5076 tumors at 45 mg/kg/day s.c. as an aqueous solution of the β-cyclodextrin complex (55% inhibition as gum arabic suspension).
IT **139406-44-3DP**, complex with 2-hydroxyethyl-β-cyclodextrin
139491-13-7DP, complex with β-cyclodextrin

Searched by: Mary Hale 571-272-2507 REM 1D86

RL: PREP (Preparation)
(preparation of, and antitumor agent)

RN 139406-44-3 HCAPLUS

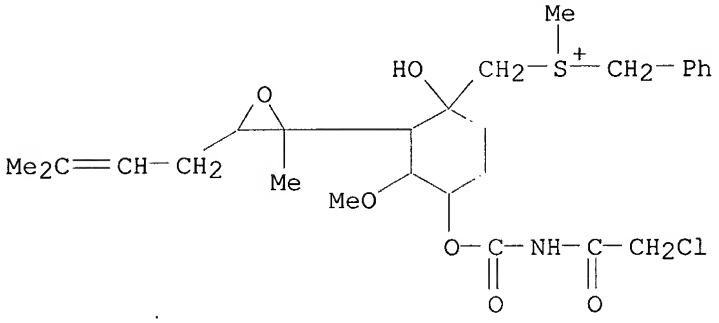
CN Beno[c]thiophenium, 2-[[4-[[[(chloroacetyl)amino]carbonyl]oxy]-1-hydroxy-3-methoxy-2-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl]methyl]-1,3-dihydro-, chloride (9CI) (CA INDEX NAME)



● Cl^-

RN 139491-13-7 HCAPLUS

CN Sulfonium, [[4-[[[(chloroacetyl)amino]carbonyl]oxy]-1-hydroxy-3-methoxy-2-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl]methyl]methyl(phenylmethyl)-, bromide (9CI) (CA INDEX NAME)



● Br^-

L4 ANSWER 19 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

1992:221566 Document No. 116:221566 Intravascular embolizing agent containing angiogenesis inhibiting substance as antitumor agents. Okada, Hiroaki; Kamei, Shigeru; Yoshioka, Toshio (Takeda Chemical Industries, Ltd., Japan). Eur. Pat. Appl. EP 470569 A1 19920212, 13 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1991-113173 19910806. PRIORITY: JP 1990-210622 19900808; JP 1991-6323 19910123.

AB Pharmaceutical compns. containing an intravascular embolizing agent and an angiogenesis-inhibiting substance are antitumor agents. The intravascular embolizing agent strengthens the antitumor effect of the angiogenesis-inhibiting substance and serves to reduce the dose and undesirable side effects. Use of the agent in combination with an angioneoplastic agent brings about further strong and long-lasting

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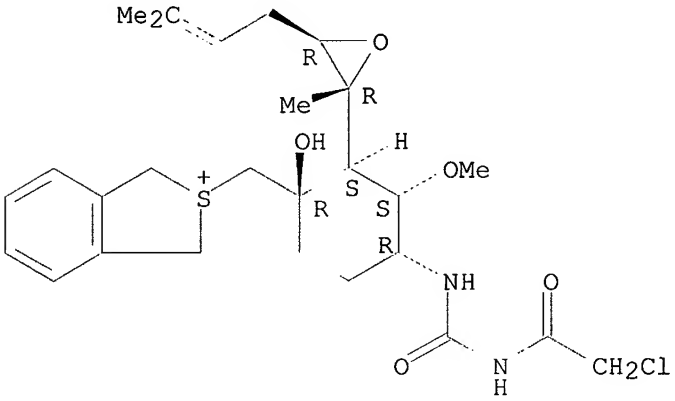
antitumor effects. Thus, 6-O-(N-chloroacetylcarbamoyl)fumagillol (I) and lactic acid-glycolic acid copolymer were dissolved in a mixture of CH2Cl2 and CHCl3 and the resultant solution was poured into aqueous solution of polyvinyl alc. and homogenized. The solvents then were evaporated and the microspheres were freeze-dried. Rabbits were transplanted s.c. with carcinogens than were injected with a dispersion of microspheres containing 1 mg I for 5 days. The volume ratio of tumor after 5 days was 36% of the control.

IT **135150-44-6**
RL: BIOL (Biological study)
(pharmaceutical composition containing intravascular embolizing agents and)

RN 135150-44-6 HCAPLUS

CN Benzo[c]thiophenium, 2-[[4-[[[(chloroacetyl)amino]carbonyl]amino]-1-hydroxy-3-methoxy-2-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl]methyl]-1,3-dihydro-, chloride, [1R-[1α,2α(2R*,3R*),3β,4.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

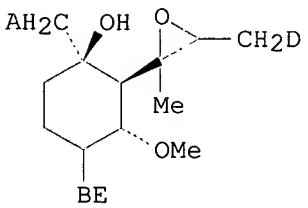


● Cl^-

L4 ANSWER 20 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

1991:471943 Document No. 115:71943 Preparation of fumagillol analogs as angiogenesis inhibitors. Kishimoto, Shoji; Marui, Shogo; Fujita, Takeshi (Takeda Chemical Industries, Ltd., Japan). Eur. Pat. Appl. EP 415294 A2 19910306, 66 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1990-116309 19900825. PRIORITY: JP 1989-226514 19890831; JP 1990-57752 19900308.

GI



I

Searched by: Mary Hale 571-272-2507 REM 1D86

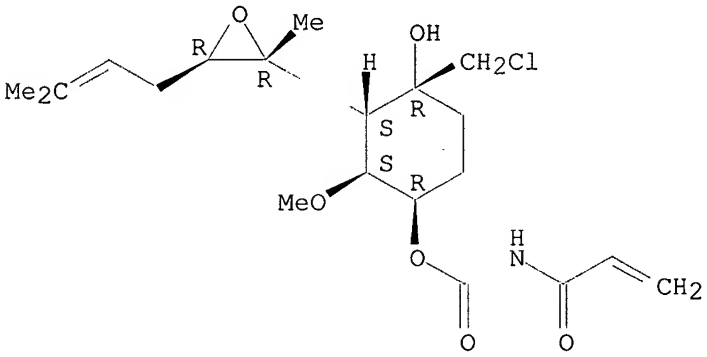
AB The title compds. [I; A = halo, NOmR1R2, N+R1R2R3X-, SOnR1, S+OmR1R2X-; R1-R3 = (un)substituted hydrocarbyl, heterocyclyl; R1R2 = atoms to complete a ring; B = O, NR4; D = CH:CMe2, CH2CHMe2; E = H, (un)substituted hydrocarbyl, acyl; R4 = H, (un)substituted alkyl, aryl; X- = anion; m = 0, 1; n = 0-2] were prepared Thus, fumagillol was treated with thiomethoxide and the product S-alkylated with 3-BrC6H4CH2Br to give I [A = 3-BrC6H4CH2S+(Me)Br-, B = β-O, D = CH:CMe2] (II; E = H) which was condensed with ClCH2CONCO to give II (E = CONHCOCH2Cl), 1 isomer of which restrained growth of tumors in mice inoculated with M5076 cells by 91% at 20 mg/kg s.c. daily for 10 days.

IT **135149-49-4P 135149-50-7P 135149-51-8P**
135149-52-9P 135149-53-0P 135149-58-5P
135149-59-6P 135149-61-0P 135149-62-1P
135149-63-2P 135149-66-5P 135149-68-7P
135149-69-8P 135149-70-1P 135149-72-3P
135149-73-4P 135149-74-5P 135149-75-6P
135149-77-8P 135149-78-9P 135149-80-3P
135149-82-5P 135149-84-7P 135149-86-9P
135149-87-0P 135149-95-0P 135149-97-2P
135150-06-0P 135150-07-1P 135150-08-2P
135150-09-3P 135150-10-6P 135150-14-0P
135150-18-4P 135150-21-9P 135150-22-0P
135150-27-5P 135150-32-2P 135150-34-4P
135150-36-6P 135150-39-9P 135150-40-2P
135150-42-4P 135150-43-5P 135150-44-6P
135150-48-0P 135150-50-4P 135150-51-5P
135150-53-7P 135194-49-9P 135194-50-2P
135268-08-5P 135268-09-6P 135268-10-9P
135268-11-0P 135269-39-5P 135269-40-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as angiogenesis inhibitor and antitumor agent)

RN 135149-49-4 HCAPLUS

CN Carbamic acid, (1-oxo-2-propenyl)-, 4-(chloromethyl)-4-hydroxy-2-methoxy-3-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl ester, [1R-[1α,2α,3β(2R*,3R*),4β]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

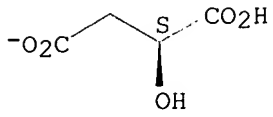


RN 135149-50-7 HCAPLUS

CN Carbamic acid, (2-methyl-1-oxo-2-propenyl)-, 4-(chloromethyl)-4-hydroxy-2-methoxy-3-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl ester, [1R-[1α,2α,3β(2R*,3R*),4β]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

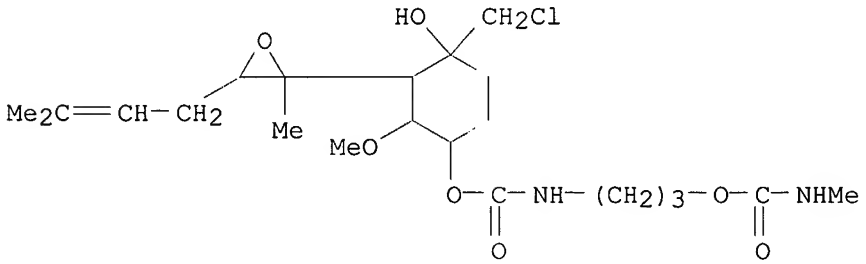
Searched by: Mary Hale 571-272-2507 REM 1D86



L4 ANSWER 21 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
1990:478423 Document No. 113:78423 Preparation of (morpholinocarbonyloxy)cyclohexanes as angiogenesis inhibitors. Oku, Teruo; Kasahara, Chiyoshi; Ohkawa, Takehiko; Hashimoto, Masashi (Fujisawa Pharmaceutical Co., Ltd., Japan). Eur. Pat. Appl. EP 354767 A1 19900214, 10 pp. DESIGNATED STATES: R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1989-308062 19890808. PRIORITY: GB 1988-19257 19880812; GB 1989-8005 19890410; GB 1989-9794 19890428.
GI

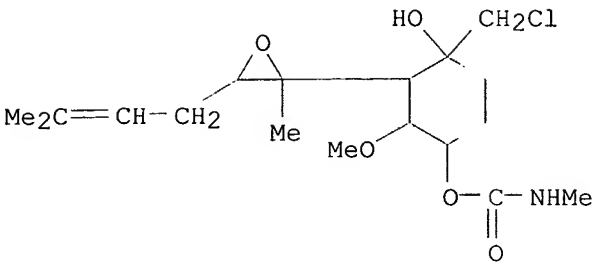
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. I (R1 = halomethyl, arylthiomethyl which may have amino, alkoxy, acylamino substituents; R2 = alkoxy; R3 = cyclopropyl groups Q1, Q2; R4 = H, alkylcarbamyl, heterocyclylcarbonyl or carbamoyl, etc.) were prepared by: a) reacting cyclohexane II with HX (X = halo, arylthio which may have amino, alkoxy, acylamino); or b) reacting cyclohexane III with an acylating agent. I are useful as drugs. 2-[2-[1-Hydroxy-1-(3-methanesulfonylaminophenylthiomethyl)-3-methoxy-4-morpholinocarbonyloxycyclohexyl]]-2-methyl-3-(3-methylbutyl)oxirane was prepared in 4 steps from 6-hydroxy-5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl-oxiranyl]-1-oxaspiro[2,5]octane. Title compound IV in vitro exhibited an IC50 of 2.1 + 10-4 μg/mL against the growth of endothelial cells from human umbilical vein.
IT **128489-17-8P 128489-18-9P 128489-19-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as angiogenesis inhibitor)
RN 128489-17-8 HCAPLUS
CN Carbamic acid, [3-[[(methylamino)carbonyl]oxy]propyl]-, 4-(chloromethyl)-4-hydroxy-2-methoxy-3-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl ester (9CI) (CA INDEX NAME)

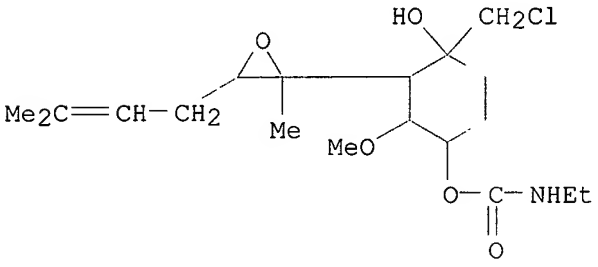


RN 128489-18-9 HCAPLUS
CN 1,4-Cyclohexanediol, 1-(chloromethyl)-3-methoxy-2-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-, 4-(methylcarbamate) (9CI) (CA INDEX NAME)

Searched by: Mary Hale 571-272-2507 REM 1D86



RN 128489-19-0 HCAPLUS
CN Carbamic acid, ethyl-, 4-(chloromethyl)-4-hydroxy-2-methoxy-3-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]cyclohexyl ester (9CI) (CA INDEX NAME)



L4 ANSWER 22 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
1984:203039 Document No. 100:203039 Stereoselective mono-oxygenation of carcinostatic 1-(2-chloroethyl)-3-(cyclohexyl)-1-nitrosourea and 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea by purified cytochrome P-450 isozymes. Potter, David W.; Levin, Wayne; Ryan, Dene E.; Thomas, Paul E.; Reed, Donald J. (Dep. Biochem. Biophys., Oregon State Univ., Corvallis, OR, 97331, USA). Biochemical Pharmacology, 33(4), 609-13 (English) 1984. CODEN: BCPCA6. ISSN: 0006-2952.

AB Three highly purified forms of liver microsomal cytochrome P-450 [9035-51-2] (P-450a, P-450b, and P-450c) from Aroclor 1254-treated rats catalyzed 1-(2-chloroethyl)-3-(cyclohexyl)-1-nitrosourea (CCNU) [13010-47-4] and 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea (MeCCNU) [33073-59-5] mono-oxygenation in the presence of purified NADPH-cytochrome P-450 reductase, NADPH, and lipid. Differences in the regioselectivity of CCNU and MeCCNU monohydroxylation reactions by the cytochrome P-450 isozymes were observed Cytochrome P-450-dependent mono-oxygenation of CCNU gave only alicyclic hydroxylation products, but mono-oxygenation of MeCCNU gave alicyclic hydroxylation products, an α-hydroxylation product on the 2-chloroethyl moiety, and a trans-4-hydroxymethyl product. A high degree of stereoselectivity for hydroxylation of CCNU and MeCCNU at the cis-4 position of the cyclohexyl ring was demonstrated. All 3 cytochrome P-450 isozymes were stereoselective in primarily forming the metabolite cis-4-hydroxy-trans-4-Methyl-CCNU **[70184-86-0]** from MeCCNU. The principal metabolite of CCNU which resulted from cytochromes P-450a and P-450b catalysis was cis-4-hydroxy CCNU [56239-24-8], whereas the principal metabolites from cytochrome P-450c catalysis were the trans-3-hydroxy [56323-44-5] and the cis-4-hydroxy isomers. Total amts. of CCNU and MeCCNU hydroxylation with cytochrome P-450b were twice that with hepatic microsomes from Aroclor 1254-treated rats. Catalysis with cytochromes P-450a and P-450c was substantially less effective than that observed with either cytochrome P-450b or hepatic microsomes from Aroclor 1254-treated rats.

IT **70184-86-0 90095-00-4**

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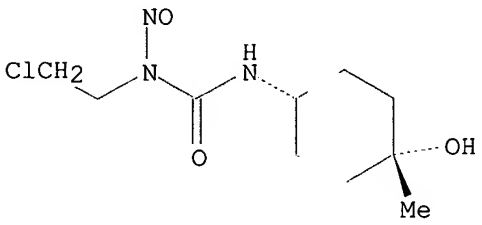
RL: FORM (Formation, nonpreparative)
(formation of, as nitrosourea metabolite, stereoselective mono-oxygenation by cytochrome P 450 in relation to)

RN 70184-86-0 HCAPLUS

CN Urea, N-(2-chloroethyl)-N'-(4-hydroxy-4-methylcyclohexyl)-N-nitroso-, cis- (9CI) (CA INDEX NAME)

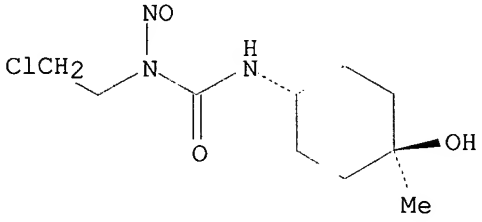
Relative stereochemistry.



RN 90095-00-4 HCAPLUS

CN Urea, N-(2-chloroethyl)-N'-(4-hydroxy-4-methylcyclohexyl)-N-nitroso-, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 23 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

1979:197339 Document No. 90:197339 Synthesis and identification of products derived from the metabolism of the carcinostatic 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea by rat liver microsomes. May, Hubert E.; Kohlhepp, Sue J.; Boose, Richard B.; Reed, Donald J. (Dep. Biochem. Biophys., Oregon State Univ., Corvallis, OR, USA). Cancer Research, 39(3), 762-72 (English) 1979. CODEN: CNREA8. ISSN: 0008-5472.

GI

I

AB Liver microsomal metabolism of the title compound I [33073-59-5] in the presence of NADPH and O was shown to produce 7 metabolites that included the parent urea. A cytochrome P-450-dependent monohydroxylation of the cyclohexyl ring occurred in 3 positions, cis-3, trans-3, and cis-4, and on the Me group to form a trans-4-hydroxymethyl derivative In addition, monohydroxylation of the 2-chloroethyl C attached to the N-1 urea N yielded an α-hydroxy metabolite. A ring-hydroxylated derivative remained unidentified, while the structures of all other such derivs. were established. Apparently, some parent urea is formed by a cytochrome P-450-dependent reaction because of a requirement for NADPH and inhibition

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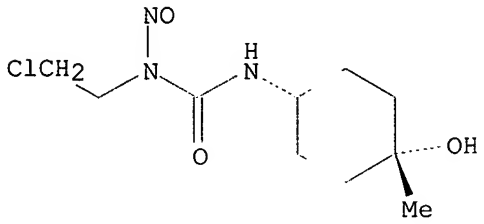
by CO. Microsomes from rats pretreated with phenobarbital showed an approx. 3-fold increase in hydroxylation rate, while phenobarbital treated mice microsomes were induced 8-fold. However, in both species, the induced hydroxylation rate was .apprx.4 nmol/min/mg protein. When microsomes from phenobarbital-induced rats were used, a mixture of 80% CO-20% O2 decreased the rate of formation of all metabolites to 14% of that in 80% N-20% O2.

IT **70184-86-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as chloroethyl(methycyclohexyl)nitrosourea metabolite)

RN 70184-86-0 HCAPLUS

CN Urea, N-(2-chloroethyl)-N'-(4-hydroxy-4-methylcyclohexyl)-N-nitroso-, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.



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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-16.79	-16.79

FILE 'CAOLD' ENTERED AT 11:22:38 ON 04 FEB 2005

FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

L6 0 L3

=> fil medl,biosis,embase,caplus;s olson g?/au;s self c?/au;s lee l?/au;s cook c?/au;s birktoft j?/au

COST IN U.S. DOLLARS	SINCE FILE	TOTAL

Searched by: Mary Hale 571-272-2507 REM 1D86

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FULL ESTIMATED COST	0.43	286.25

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
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FILE 'BIOSIS' ENTERED AT 11:23:25 ON 04 FEB 2005

FILE 'EMBASE' ENTERED AT 11:23:25 ON 04 FEB 2005

FILE 'CAPLUS' ENTERED AT 11:23:25 ON 04 FEB 2005

L7	393	FILE MEDLINE
L8	649	FILE BIOSIS
L9	327	FILE EMBASE
L10	848	FILE CAPLUS
TOTAL FOR ALL FILES		
L11	2217	OLSON G?/AU
L12	59	FILE MEDLINE
L13	98	FILE BIOSIS
L14	54	FILE EMBASE
L15	97	FILE CAPLUS
TOTAL FOR ALL FILES		
L16	308	SELF C?/AU
L17	2198	FILE MEDLINE
L18	2864	FILE BIOSIS
L19	1806	FILE EMBASE
L20	3469	FILE CAPLUS
TOTAL FOR ALL FILES		
L21	10337	LEE L?/AU
L22	849	FILE MEDLINE
L23	1180	FILE BIOSIS
L24	658	FILE EMBASE
L25	1086	FILE CAPLUS
TOTAL FOR ALL FILES		
L26	3773	COOK C?/AU
L27	53	FILE MEDLINE
L28	70	FILE BIOSIS
L29	37	FILE EMBASE
L30	63	FILE CAPLUS

Searched by: Mary Hale 571-272-2507 REM 1D86

TOTAL FOR ALL FILES
L31 223 BIRKTOFT J?/AU

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L32 0 FILE MEDLINE
L33 1 FILE BIOSIS
L34 0 FILE EMBASE
L35 4 FILE CAPLUS

TOTAL FOR ALL FILES
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L38 0 FILE BIOSIS
L39 0 FILE EMBASE
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TOTAL FOR ALL FILES
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PROCESSING COMPLETED FOR L36
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L42 ANSWER 1 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
2003:227301 Document No.: PREV200300227301. Therapeutic agents and methods of use thereof for the modulation of angiogenesis. **Olson, Gary L.** [Inventor, Reprint Author]; **Self, Christopher** [Inventor]; **Lee, Lily** [Inventor]; **Cook, Charles Michael** [Inventor]; **Birktoft, Jens J.** [Inventor]. Mountainside, NJ, USA. ASSIGNEE: Praecis Pharmaceuticals Inc., Waltham, MA, USA. Patent Info.: US 6548477 April 15, 2003. Official Gazette of the United States Patent and Trademark Office Patents, (Apr 15 2003) Vol. 1269, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.

AB The present invention provides angiogenesis inhibitor compounds comprising a MetAP-2 inhibitory core coupled to a peptide, as well as pharmaceutical compositions comprising the angiogenesis inhibitor compounds and a pharmaceutically acceptable carrier. The present invention also provides methods of treating an angiogenic disease, e.g., cancer, in a subject by administering to the subject a therapeutically effective amount of one or more of the angiogenesis inhibitor compounds of the invention.

L42 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
2003:455053 Document No. 139:7179 Preparation of compounds comprising a methionine aminopeptidase 2 (MetAP-2) inhibitory core coupled to a peptide for modulation of angiogenesis. **Olson, Gary L.; Self, Christopher; Lee, Lily; Cook, Charles Michael; Birktoft, Jens;** Morgan, Barry; Arico-Muendel, Christopher C. (Praecis Pharmaceuticals Inc., USA). U.S. Pat. Appl. Publ. US 2003109671 A1 20030612, 48 pp., Cont.-in-part of U.S. Ser. No. 1,945. (English). CODEN: USXXCO. APPLICATION: US 2002-138935 20020502. PRIORITY: US 2000-704251 20001101; US 2001-972772 20011005; US 2001-1945 20011101.

AB The invention provides angiogenesis inhibitor compds. A-W-CONR1-Xn-CR3R4-Z-P [A is a Met-AP-2 inhibitory core; W is O or NR2; R1, R2 are H or alkyl; X is alkylene or substituted alkylene; n is 0 or 1; R3, R4 are H, (un)substituted alkyl or (hetero)aryl; or CR3R4 is carbocyclic, heterocyclic, or alkylene; Z is CO or alkylene-CO and P is a peptide comprising 1 to about 100 amino acid residues attached at its amino

terminus to Z or a group OR5 or NR6R7, where R5-R7 are H, alkyl, (un)substituted alkyl or azacycloalkyl or NR6R7 is (un)substituted heterocyclyl; or Z is O, NR6 (R8 = H or alkyl), alkylene-O, or alkylene-NR8 and P is H, alkyl or a peptide consisting of 1 to about 100 amino acid residues attached at its carboxy terminus to Z] comprising a MetAP-2 inhibitory core coupled to a peptide, as well as pharmaceutical compns. comprising the angiogenesis inhibitor compds. Thus, (3R,4S,5S,6R)-5-methoxy-4-[(2R, 3R)-2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-ylcarbonyl-L-valine Me ester, prepared by acylation of L-valine Me ester hydrochloride, showed IC50 = 4.7 nM for inhibition of MetAP-2.

L42 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

2002:408668 Document No. 136:402029 Preparation of amino acid compounds containing the fumagillin core for the modulation of angiogenesis. **Olson, Gary L.; Self, Christopher; Lee, Lily; Cook, Charles Michael; Birktoft, Jens** (Praecis Pharmaceuticals Inc., USA). PCT Int. Appl. WO 2002042295 A2 20020530, 98 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US46086 20011101. PRIORITY: US 2000-704251 20001101; US 2001-972772 20011005.

AB Compds. A-W-CONR1-Xn-CR3R4-Z-P [A is a Met-AP2 inhibitory core; W = O or NR2; R1, R2 = H or alkyl; X = alkylene or substituted alkylene; n = 0 or 1; R3, R4 = H, (un) alkyl, aryl or heteroaryl; R3R4 = alkylene or R3R4C is a carbocyclic or heterocyclic group; Z = CO or alkylene-CO-; P is a peptide comprising 1.apprx.100 amino acid residues attached at its amino terminus to Z or a group OR5 or NR6R7, where R5, R6, R7 are H, (un)substituted alkyl or azacycloalkyl or R6R7N = (un)substituted heterocyclyl] were prepared for treating an angiogenic disease, e.g., cancer. Title angiogenesis inhibitor compds. have excellent MetAP2 inhibitory activity and are able to inhibit endothelial cell growth at the picomolar range. Thus, Q-CO-D-Val-Me (Q is the alc. derived from fumagillin) was prepared via amidation reaction and showed IC50 = 4.7 nM in MetAP2 assay.

L42 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

2002:965105 Document No. 138:33374 Therapeutic agents and methods of use thereof for the modulation of angiogenesis. **Olson, Gary L.; Self, Christopher; Lee, Lily; Cook, Charles Michael; Birktoft, Jens** (Praecis Pharmaceuticals Inc., USA). U.S. Pat. Appl. Publ. US 2002193298 A1 20021219, 38 pp., Cont.-in-part of U. S. Ser. No. 704,251. (English). CODEN: USXXCO. APPLICATION: US 2001-972772 20011005. PRIORITY: US 2000-704251 20001101.

AB The present invention provides angiogenesis inhibitor compds. comprising a MetAP-2 (methionine aminopeptidase-2)-inhibitory fumagillin core coupled to a peptide, as well as pharmaceutical compns. comprising the angiogenesis inhibitor compds. and a pharmaceutically acceptable carrier. The present invention also provides methods of treating an angiogenic disease, e.g., cancer, in a subject by administering to the subject a therapeutically effective amount of one or more of the angiogenesis inhibitor compds. of the invention.

L42 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

2002:794303 Document No. 137:311201 Preparation of amino acid compounds containing the fumagillin core for the modulation of angiogenesis.

Searched by: Mary Hale 571-272-2507 REM 1D86

Olson, Gary L.; Self, Christopher; Lee, Lily; Cook, Charles Michael; Birktoft, Jens; Morgan, Barry; Arico-muendel, Christopher C. (Praecis Pharmaceuticals Inc., USA). U.S. Pat. Appl. Publ. US 2002151493 A1 20021017, 47 pp., Cont.-in-part of U. S. Ser. No. 972,772. (English). CODEN: USXXCO. APPLICATION: US 2001-1945 20011101. PRIORITY: US 2000-704251 20001101; US 2001-972772 20011005.

AB Compds. A-W-CONR1-Xn-CR3R4-Z-P [A is a Met-AP2 inhibitory core; W = O or NR2; R1, R2 = H or alkyl; X = alkylene or substituted alkylene; n = 0 or 1; R3, R4 = H, (un)alkyl, aryl or heteroaryl; R3R4 = alkylene or R3R4C is a carbocyclic or heterocyclic group; Z = CO or alkylene-CO-; P is a peptide comprising 1.apprx.100 amino acid residues attached at its amino terminus to Z or a group OR5 or NR6R7, where R5, R6, R7 are H, (un)substituted alkyl or azacycloalkyl or R6R7N = (un)substituted heterocyclyl; or Z = O, NR8, alkylene-O, alkylene-NR8, where R8 = H or alkyl and P = H, alkyl, or a peptide] were prepared for treating an angiogenic disease, e.g., cancer. Title angiogenesis inhibitor compds. have excellent MetAP2 inhibitory activity and are able to inhibit endothelial cell growth at the picomolar range. Thus, Q-CO-D-Val-Me (Q is the alc. derived from fumagillin) was prepared via amidation reaction and showed IC50 = 4.7 nM in MetAP2 assay.

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L43           0 FILE MEDLINE
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L45           0 FILE EMBASE
L46           0 FILE CAPLUS

TOTAL FOR ALL FILES
L47           0 (L11 OR L16 OR L21 OR L26 OR L31) AND L3

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L1               STR
L2             7 S L1
L3           127 S L1 FUL

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                E ANGIOGENSIS/CT
L5             0 S L4 AND ANGIOGENS?

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L6             0 S L3

     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 11:23:25 ON 04 FEB 2005
L7           393 FILE MEDLINE
L8           649 FILE BIOSIS
L9           327 FILE EMBASE
L10          848 FILE CAPLUS
     TOTAL FOR ALL FILES
L11         2217 S OLSON G?/AU
L12           59 FILE MEDLINE
L13           98 FILE BIOSIS
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L16          308 S SELF C?/AU
L17         2198 FILE MEDLINE
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Searched by: Mary Hale 571-272-2507 REM 1D86

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L18         2864 FILE BIOSIS
L19         1806 FILE EMBASE
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     TOTAL FOR ALL FILES
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L30           63 FILE CAPLUS
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L39            0 FILE EMBASE
L40            0 FILE CAPLUS
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L43            0 FILE MEDLINE
L44            0 FILE BIOSIS
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L46            0 FILE CAPLUS
     TOTAL FOR ALL FILES
L47            0 S (L11 OR L16 OR L21 OR L26 OR L31) AND L3

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DELETE ALL L# ITEMS? (Y)/N:y


COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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FULL ESTIMATED COST                                      34.66     320.91

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                      -2.92     -19.71

FILE 'REGISTRY' ENTERED AT 11:24:50 ON 04 FEB 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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STRUCTURE FILE UPDATES:    2 FEB 2005  HIGHEST RN 824932-81-2
DICTIONARY FILE UPDATES:   2 FEB 2005  HIGHEST RN 824932-81-2

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004


Searched by: Mary Hale 571-272-2507 REM 1D86
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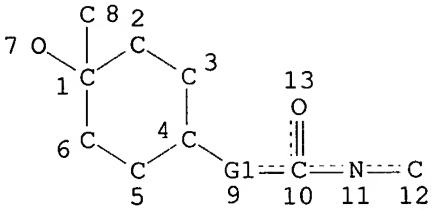

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 13

STEREO ATTRIBUTES: NONE
L3 127 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 1834 ITERATIONS 127 ANSWERS
SEARCH TIME: 00.00.01

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	162.19	162.40

FILE 'HCAPLUS' ENTERED AT 11:20:28 ON 04 FEB 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 4 Feb 2005 VOL 142 ISS 6
FILE LAST UPDATED: 2 Feb 2005 (20050202/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

L4 23 L3

=> e angiogensis/ct
E# FREQUENCY AT TERM

Searched by: Mary Hale 571-272-2507 REM 1D86